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IMIDAZOLE-CONTAINING DIARYLETHER AND DIARYLSULFONE INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

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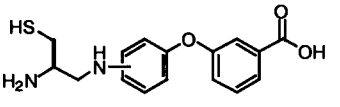
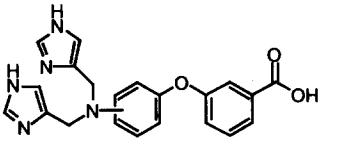
Abstract: The design and syntheses of non-thiol inhibitors of farnesyl-protein transferase are described. Optimization of cysteine-substituted diarylethers led to highly potent imidazole-containing diarylethers and diarylsulfones. Polar diaryl linkers dramatically improved potency and gave highly cell active compounds. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Oncogenically activated Ras protein has been implicated in the growth of 20–30% of all human tumors.[1] In tumor cells, altered Ras loses its normal GTPase function, becomes constitutively bound to GTP, and transmits growth signals independent of extracellular growth factors to downstream mitogenic effectors.[2] Strategies for regulating unimpeded oncogenic *ras* signalling have focused on preventing the prenylation of Ras by inhibition of farnesyl-protein transferase (FTase), a zinc metalloenzyme which catalyzes the lipidation of a cysteine in the C-terminal tetrapeptide sequence.[3,4] FTase inhibitors (FTIs) have been shown to selectively inhibit *ras*-transformed cell growth in cell culture,[5] and to inhibit the growth of *ras*-dependent tumors in mice.[6]

A wide array of inhibitors of FTase that mimic the tetrapeptide C-terminus of Ras (the Ca_1a_2X motif)[7] have been described.[8] Improvements in the biological properties of FTIs have been achieved with the use of non-peptide structural replacements for the central a_1a_2 portion, the deletion of the carboxyl-containing terminus, and substitution of the cysteine moiety with alternative non-thiol groups.[8] Notably, nitrogen heterocycles are alternatives to the cysteine thiol in various structural classes, perhaps due to their ability to bind a zinc atom at the enzyme active site.[9] In a previous approach toward pharmacologically acceptable FTIs, we investigated the diarylether as an a_1a_2X surrogate (e.g., **1a,b**).[10] In this paper, we describe the optimization of diarylether FTIs by incorporating an imidazole ring and other features that lead to highly potent and cell-active inhibitors.



1a *meta*
1b *para*



2a *meta*
2b *para*

Initial evaluation of imidazole-substituted diarylethers **2a** (IC_{50} = 19 μM) and **2b** (IC_{50} = 2.6 μM) revealed a significant decrease in potency relative to the parent cysteinyl derivatives **1a** (IC_{50} = 0.25 μM) and **1b** (IC_{50} = 0.40 μM), as well as a several-fold preference for the *para*-substitution pattern. Since it had been

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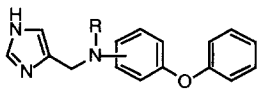
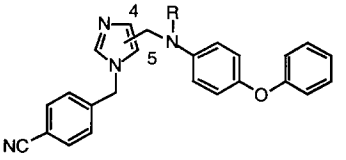
discovered earlier that the carboxyl group in the cysteinyl diarylethers (e.g. **1**) contributed little to in vitro FTase activity,[10] attention was turned toward optimization of non-carboxylate analogs of **2**. An earlier investigation of nonthiol 3-aminomethylbenzamide-methionine FTIs suggested that replacement of one of the imidazolylmethyl groups in **2** with an alkyl or substituted benzyl group would enhance potency.[11] These considerations prompted a series of FTIs based on the parent mono-imidazole diarylether template **3a** (Table 1). While substitution on **3a** with an *n*-alkyl chain was insufficient to confer measurable inhibitory activity (**3b**), the *p*-nitrobenzyl group provided the anticipated potency increase (**3c**, IC_{50} = 1.0 μM). This result is in accord with an earlier report which established the presence of a high-affinity aromatic binding pocket near the cysteine binding region of FTase.[12] Consistent with the comparison of **2b** vs **2a**, the *meta*-isomer **4** (IC_{50} = 3.2 μM) was several-fold less active than *para*-isomer **3c**. For this reason, further optimization was carried out on *para*-substituted analogs.

Table 1



compd	isomer	R	IC_{50} (nM)[a]
3a	*para*	H	>100,000
3b	*para*	*n*-Bu	>100,000
3c	*para*	4-(NO_2)benzyl	1,000
4	*meta*	4-(NO_2)benzyl	3,200

Table 2



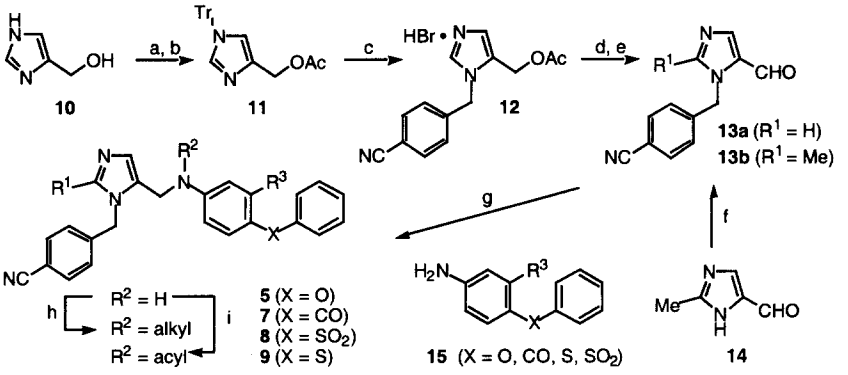
compd	isomer	R	IC_{50} (nM)[a]
5a	*C*-5	H	1,300
5b	*C*-5	*n*-Bu	42
5c	*C*-5	4-(CN)benzyl	8
6	*C*-4	*n*-Bu	>100,000

(a) Concentration of compound required to reduce the FTase-catalyzed incorporation of [^{3}H]FPP into recombinant Ha-Ras by 50%. Enzyme purified from bovine brain at ca. 1 nM was used, as described in ref 5a.

It had been demonstrated in prior work that optimal juxtaposition of the imidazole and aromatic moieties for binding to FTase could be achieved using the 1-(4-cyanobenzyl)-5-imidazolyl template.[13] Thus, the performance of this cysteine replacement in the context of the present diarylethers was investigated (Table 2). The parent compound **5a** (IC_{50} = 1.3 μM), juxtaposed with inactive **3a**, revealed the importance of the cyanobenzyl group. On derivatization of the exocyclic amine in **5a**, it was found that 30-fold potency was gained by the addition of an alkyl chain (**5b**, IC_{50} = 42 nM), and 160-fold was gained with a second cyanobenzyl group (**5c**, IC_{50} = 8 nM). The migration of the cyanobenzyl group from proximal to distal nitrogen on the imidazole ring was dramatically deleterious to FTase inhibition (**6** = inactive; **5b** = 42 nM), indicating sensitivity to the relative positioning of the cyanobenzyl and diarylether moieties, and/or the importance of the imidazole *N*-3 as a putative binding element to an active site zinc atom. Compound **5c**, the most potent diarylether FTI in the series, was evaluated for activity in cell culture. Inhibition of v-Ha-*ras* transformed RAT1 cell growth in soft agar was observed at submicromolar levels (MIC = 0.25–1 μM), and posttranslational prenylation of Ha-Ras protein in cultured NIH3T3 cells was inhibited[5c] with an IC_{50} of 1–10 μM. In the control studies to demonstrate selectivity, *raf*-transformed cell growth was uninhibited by **5c** below 2.5 μM concentration in soft agar, and much higher concentration of was required to engender cellular cytotoxicity in RAT1 cells (CTE = 50 μM) as assessed by viable staining with MTT.

To expedite further development of the 1-cyanobenzyl-5-imidazolyl substituted diarylether series, a simple convergent synthesis strategy was employed (Scheme 1). The imidazole carboxaldehyde **13a** was available from 4-hydroxymethylimidazole **10** by a protection-alkylation-deprotection sequence (**11**→**12**), followed by oxidation. The 2-methylimidazole **13b** was prepared directly from a moderately selective alkylation of **14**. Aldehydes **13a** and **13b** were reductively coupled[14] to anilines **15** to provide products that could then be further functionalized on the exocyclic nitrogen to give the final compounds **5** and **7–9**.

Scheme 1

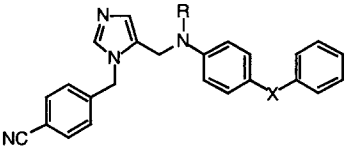


(a) TrCl, Et_3N, DMF. (b) Ac_2O, pyridine. (c) 4-(CN)BnBr, EtOAc, 60 °C; MeOH, 60 °C. (d) LiOH, $THF–H_2O$. (e) SO_3•Pyridine, Et_3N, DMSO (f) 4-(CN)BnBr, Cs_2CO_3, DMF, 0 °C; separate isomers (ca. 2:1). (g) $Na(AcO)_3BH$, AcOH, 4 Å MS, $ClCH_2CH_2Cl$, 0 °C–rt. (h) aldehyde, $Na(AcO)_3BH$, 4 Å MS, $ClCH_2CH_2Cl$, 0 °C–rt. (i) *n*-BuLi, THF; *c*-PrCOCl, 0 °C–rt.

Investigation of diarylether oxygen atom replacements led to the discovery that polar diaryl linkers dramatically increased potency (Table 3). Simple exchange of oxygen in **5a** for carbonyl (**7**, IC_{50} = 0.8 nM) or sulfonyl (**8a**, IC_{50} = 0.7 nM) provided subnanomolar compounds. In contrast, the ether to thioether permutation resulted in only a three-fold change (**5b** = 42 nM; **9** = 140 nM). The 1800-fold shift in potency for **8a** relative to The parent ether suggests a possible interaction with a hydrogen bond donor in the enzyme active site (*vide infra*).

Further optimization of diarylsulfone **8a** included substitutions on the imidazole ring, the exocyclic nitrogen, and the central aromatic ring (Table 4). While addition of a methyl group to the imidazole 2-position caused a 100-fold drop in IC_{50} (**8b**; 93 nM), substitution adjacent to the sulfonyl group had no influence (**8c**; 1 nM). Interestingly, incorporation of both substitutions simultaneously gave the unexpectedly potent **8d** (IC_{50} = 0.45 nM). Also unexpected was that *N*-alkylation (R^2) with a hydrophobic group, a potency enhancing feature in the diarylether series (e.g. Table 2), did not cause the desired effect in the diarylsulfones. While addition of a cyclopropylmethyl group to **8d** resulted in the 20 fold less active **8e** (IC_{50} = 8 nM), acylation to give **8f** was even

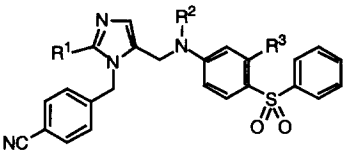
Table 3



compd	R	X	IC_{50} (nM)[a]
5a	H	O	1,300
7	H	CO	0.8
8a	H	SO_2	0.7
5b	*n*-Bu	O	42
9	*n*-Bu	S	140

(a) See corresponding footnote in Table 1. For IC_{50}, < 1 nM, enzyme concentration was 10 pM in the assay.

Table 4



compd	R^1	R^2	R^3	IC_{50} (nM) FTase[a]	IC_{50} (nM) H-*ras* poly(HEMA)[b]
8a	H	H	H	0.7	31
8b	Me	H	H	93	177
8c	H	H	Me	1	16
8d	Me	H	Me	0.45	28
8e	Me	CH_2-*c*-Pr	Me	8	109
8f	Me	CO-*c*-Pr	Me	232	nd
8g	Me	4-(CN)benzyl	H	81	nd

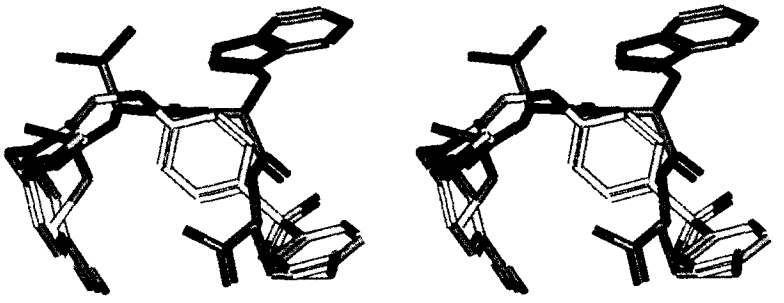
(a) See corresponding footnote in Table 2. (b) Concentration required to inhibit by 50% the anchorage-independent proliferation of RAT1 v-Ha-*ras* transformed cells on poly-(HEMA)-coated plates relative to vehicle-treated control. Assay conditions were modified from ref 15b. "nd" = not determined.

worse (IC_{50} = 232 nM). Attachment of a 4-cyanobenzyl group gave **8g** (IC_{50} = 81 nM), which was equipotent to its unsubstituted analog **8b**. The disparity between SAR in the diarylether and diarylsulfone series suggests that aspects of their binding modes are distinctly different.

The successful design of subnanomolar inhibitors from the diarylsulfone series prompted an evaluation of their in vivo cell activities (Table 4). An assay[15] to quantitate anchorage-independent growth of *Ha*-ras transformed Rat1 cells on poly-(HEMA) coated microtiter plates revealed a correlation between in vitro inhibition of FTase activity and inhibition of cell growth. This suggests that the mechanism of cell growth inhibition is directly related to inhibition of FTase, not the result of a general cytotoxic effect. Compound **8c** was the most potent in cell culture (IC_{50} = 16 nM), with 16-fold disparity between its in vivo and in vitro activities. Since the less active FTIs showed a lower ratio of cell culture and in vitro IC_{50}s (e.g., **8b** ratio = 2) relative to the more active derivatives (e.g., **8d** ratio = 62), it is likely that the latter are less cell penetrant.

A hypothesis for the enzyme-bound conformation of the diarylsulfones is provided by an overlay of energy-minimized **8a** onto the previously characterized structure of an FTase-bound inhibitor. The Ca_1a_2X peptide sequence CVWM (IC_{50} = 525 nM) had been found by ^1H NMR transferred NOE spectroscopy to adopt a conformation most closely approximating a type III β-turn when specifically bound to the FTase enzyme (see Figure 1).[16] A best-fit superposition[17] of **8a** onto the CVWM structure may account for key aspects of the structure activity relationships (SAR). The position-3 nitrogen atom of the imidazole ring, assumed to perform a zinc-ligating function, lies in the region occupied by the cysteine thiol group of CVWM. The *para*-disubstituted phenyl ring of **8a** serves as a rigid spacer with appropriate length to position the terminal phenylsulfonyl group in the region occupied by the C-terminus of the peptide. The phenyl moiety overlays well

Figure 1 Best-fit superposition (cross-eyed stereoview) of compound **8a** (gray) and the FTase-bound conformation of CVWM (green) as determined by ^{1}H NMR transferred NOE spectroscopy (ref 16). Hydrogens have been omitted for clarity.



with the lipophilic methionine side chain, while one of the sulfone oxygens is in register with that of the tryptophan carbonyl. Functional homology between the sulfonyl group and the a_2-backbone carbonyl of the Ca_1a_2X sequence seems plausible, since reductions in polarity at both the sulfone position of **8a** (see Table 3) and the a_2-carbonyl of a Ca_1a_2X sequence (e.g., $a_2[\psi CH_2NH]$)[18] significantly reduce inhibitory activity. The sulfone may serve as a hydrogen bond acceptor in the enzyme active site. The terminal 4-cyanobenzyl group attached to imidazole reaches into a high-affinity aromatic binding pocket of undefined location,[12] which is not accessed by CVWM. As noted earlier, increases in potency by substitution on the anilinic nitrogen atom were dependent on the identity of the diaryl-linking group. While the strategy was successful in giving more potent diarylethers (e.g., **5b** vs. **5a**, Table 2), no such benefit was conferred to the diarylsulfones (Table 4). It is hypothesized that the absence of the hydrogen bond accepting (sulfonyl) group permitted the diarylethers to bind in a manner that optimizes interaction of the hydrophobic nitrogen substituent with the a_1-hydrophobic (valine side-chain) pocket in FTase. Constraint of the position of the sulfonyl group in **8a** (Figure 1), perhaps to maximize hydrogen bonding, may induce the suboptimal placement of a hydrophobic substituent on nitrogen and thus compromise an otherwise favorable interaction with the a_1-hydrophobic pocket.

The design and synthesis of imidazole-substituted diaryl-X compounds have led to highly potent nonthiol farnesyltransferase inhibitors. Introduction of the polar sulfone linker gave subnanomolar FTIs that were highly potent in cell culture, enabling the reversal of anchorage-independent growth of H-*ras* transformed cells at low concentration.

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